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Original Article

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Growth in Infants with Cow's Milk Protein Allergy Fed an Amino Acid-Based Formula

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ABSTRACT

Purpose: The present study assessed the role of an amino acid-based formula (AAF) in the growth of infants with cow's milk protein allergy (CMPA).
Methods: Non-breastfed, term infants aged 0–6 months with symptoms suggestive of CMPA were recruited from 10 pediatric centers in China. After enrollment, infants were started on AAF for two weeks, followed by an open food challenge (OFC) with cow's milk-based formula (CMF). Infants with confirmed CMPA remained on AAF until 9 months of age, in conjunction with a cow's milk protein-free complementary diet. Body weight, length, and head circumference were measured at enrollment and 9 months of age. Measurements were converted to weight-for-age, length-for-age, and head circumference-for-age Z scores (WAZ, LAZ, HCAZ), based on the World Health Organization growth reference.
Results: Of 254 infants (median age 16.1 weeks, 50.9% male), 218 (85.8%) were diagnosed with non-IgE-mediated CMPA, 33 (13.0%) tolerated CMF, and 3 (1.2%) did not complete the OFC. The mean WAZ decreased from 0.119 to −0.029 between birth and enrollment (p=0.067), with significant catch-up growth to 0.178 at 9 months of age (p=0.012) while being fed the AAF. There were no significant changes in LAZ (0.400 vs. 0.552; p=0.214) or HCAZ (−0.356 vs. −0.284; p=0.705) from the time of enrollment to age 9 months, suggesting normal linear and head growth velocity.
Conclusion: The amino acid-based study formula, in conjunction with a cow's milk protein-free complementary diet, supported normal growth till 9 months of age in a cohort of Chinese infants with challenge-confirmed non-IgE-mediated CMPA.

Keywords: Anthropometry; Food hypersensitivity; Nutrition; Infant formula; Challenge test

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Conflict of Interest
YV has participated as a clinical investigator, advisory board member, consultant and/or speaker for Abbott Nutrition, Biocodex, Danone, Mead Johnson, Merck, Menarini, Nestlé Health Science, Nestlé Nutrition Institute, Nutricia, Phacobel, Sari Husada, Sucampo, United Pharmaceuticals, Yakult, and Chr. Hansen. CD has received honoraria as an advisory board member, consultant, and/or speaker from Danone, Nestlé Health Science, Sodilac, United Pharmaceuticals, and is a shareholder of DBV Technologies. PE has received lecture honoraria from Danone and Sodilac and research grants from Nestlé. AH has received honoraria for lectures in Danone and Nestlé. CR-K has participated as a consultant and/or speaker for Mead Johnson International, Hero Institute, Alter-Nutriben, Danone, and Nestlé. HS has participated as a clinical investigator and/or speaker for Arla, Danone, Nestlé, Nestlé Nutrition Institute, Nutricia, and Mead Johnson. AJ and RGH are employees of Nestlé Health Science.

INTRODUCTION

Cow's milk protein allergy (CMPA) is the most common food allergy in infancy [1,2]. The reported worldwide prevalence of CMPA varies between 0.7 to 2.7% [2-5]. Symptoms of immediate-type CMPA (IgE-mediated) include urticaria, lip swelling, facial angioedema, and in extreme cases, anaphylaxis [6]. By contrast, non-IgE-mediated CMPA presents in infancy with a range of gastrointestinal and systemic manifestations, including vomiting or regurgitation, diarrhea, rectal bleeding, feeding difficulties, persistent crying, and sleep problems [7]. Conditions with a mixed IgE- and non-IgE-mediated etiology, such as atopic eczema and eosinophilic esophagitis, are also frequently associated with CMPA [8-10].

The treatment of CMPA relies on strict dietary elimination of cow's milk protein (CMP) from the infant's diet [11]. In symptomatic breastfed infants, a maternal elimination diet may also be helpful [12]. In formula-fed infants, the management of CMPA generally involves the use of an extensively hydrolyzed formula (EHF) or an amino acid-based formula (AAF) [11,13]. While EHF is considered the first-line formula of choice in the management of infants with mild to moderate CMPA symptoms, AAF is generally prescribed to infants with moderate to severe symptoms, including those with a history of anaphylaxis, growth failure, or eosinophilic esophagitis [11,14,15].

Several studies have suggested that, compared to healthy children, growth in children with food allergies is often impaired, and the etiology is multifactorial [16,17]. Causative factors include prolonged dietary restrictions as part of a single or multiple allergen avoidance, associated feeding difficulties, and atopic comorbidities, rather than differences in energy expenditure or nutritional needs [18-21]. Moreover, infants and young children receiving an unsupervised cow's milk exclusion diet have an increased risk of micronutrient deficiencies, mainly due to insufficient iron, calcium, and vitamin B12 intake [17,22].

Growth studies for AAF have traditionally been conducted in healthy infants between 0 and 4 months of age to assess the growth parameters in a well-defined population that is fed exclusively with the study formula, either comparing growth to breastfed infants or a control group receiving another reference formula [23-26]. Several growth studies have been conducted in the target population of infants with CMPA [27-30]. While this approach may be more relevant clinically, the interpretation may be confounded by age and complementary diet. Overall, these studies have shown that AAF supports adequate growth and nutrition in children with CMPA. Data on long-term growth outcomes in infants with CMPA who are managed with an AAF are limited, highlighting a need for further studies in the target population [29]. The abovementioned studies were conducted in North America or Europe, and no dedicated growth studies are currently available for Asian infants. As part of a validation study for the Cow's Milk-related Symptom Score (CoMiSS™) [31], we prospectively evaluated anthropometric parameters in a cohort of Chinese infants with challenge-confirmed CMPA. The objective of the present study was to assess whether AAF supports normal growth in infants with CMPA up to 9 months of age, in conjunction with a CMP-free complementary diet.

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MATERIALS AND METHODS

Non-breastfed infants aged 0–6 months with symptoms suggestive of CMPA (e.g., eczema, irritability, feeding problems, vomiting/regurgitation, persistent diarrhea, rectal bleeding) were recruited from 10 clinical centers in China. After a baseline assessment, the infants were started on a strict CMP-free elimination diet with an AAF (Alfamino®; Nestlé Health Science, Vevey, Switzerland) for two weeks. In infants above 4 months of age, a CMP-free complementary diet was allowed during the trial. After 2 weeks on the elimination diet, infants underwent a standardized open food challenge (OFC) with a cow's milk-based infant formula (CMF, Nestlé NAN1®; Nestlé Nutrition) [32]. Infants who developed clinical symptoms during the challenge with CMF were diagnosed with CMPA and were offered to remain on the AAF until 9 months of age. Infants who did not have symptoms on the Day 1 of OFC in the hospital, were subsequently assessed by a two-week home challenge with CMF. Infants who reacted during the home challenge phase were reviewed, and a diagnosis of CMPA was made if symptoms were consistent. The parents of these infants were advised to recommence AAF feeding. Infants who passed both the hospital and home challenges without adverse symptoms returned to an unrestricted diet and were discharged from the study.

Weight, length, and head circumference (HC) were measured at enrollment and final follow-up at around 9 months of age. In addition, birth weight and length were also documented. Body weight was measured on calibrated digital scales, with the infant unclothed and recorded to the nearest 5 grams. Length was measured in a supine position on standardized length boards and recorded to the nearest 1 millimeter (mm). HC was measured with a non-elastic tape and recorded to the nearest 1 mm. Weight-for-age, length-for-age, and head circumference-for-age Z scores (WAZ, LAZ, and HCAZ) were calculated based on the World Health Organization (WHO) growth reference. Descriptive statistics (percentage, mean, median, standard deviation, and 95% confidence intervals) were used to summarize the data.

Study formula

The study AAF was a nutritionally complete powdered infant formula containing amino acids (protein equivalent 1.9 g/100 mL), carbohydrates (7.9 g/100 mL), fats (3.4 g/100 mL, 24% medium chain triglycerides [MCT] of total fat content), vitamins, minerals, trace elements, long-chain polyunsaturated fatty acids, arachidonic acid (7.0 mg/100 mL), and docosahexaenoic acid (7.0 mg/100 mL). A previous clinical trial had confirmed that the study formula was hypoallergenic and suitable for the nutritional management of infants with CMPA [33]. During the study period, the formula was prepared by the infant's caregiver according to standard instructions provided on the container.

Open oral food challenge procedure

The open oral food challenge was performed in the hospital on Day 1, followed by an open home challenge for 2 weeks, if tolerated [32]. The hospital challenge was supervised by a medically qualified study investigator. All investigators were trained in the food challenge procedures. This training included watching a detailed training video in Chinese. The OFC followed a standardized dose escalation of CMF with careful documentation of any clinical symptoms that developed during the challenge period. The following doses of CMF were administered during the OFC: initial test dose of one drop on the lip of the infant; if no reaction was observed after 15 minutes, then 0.5 mL was given orally. If no reaction was observed after 30 minutes, the following oral doses were administered at 30 minutes intervals: 1 mL, 3 mL, 10 mL, 30 mL, 50 mL, and 100 mL (maximum cumulative dose: 194.5

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mL), based on the tolerance of the infant. The challenge was categorized as 'positive' or 'negative' by the investigator according to pre-defined end criteria, based on the observed symptoms. The OFC was considered positive in the presence of immediate symptoms (vomiting, urticaria, facial angioedema, wheeze, or stridor) during Day 1 in hospital or delayed-onset symptoms (vomiting, increased regurgitation, persistent diarrhea, increased eczema, or irritability/persistent crying) at any time during the home challenge phase of two weeks [32]. Parents were asked to report any possible clinical reaction during the home challenge. The reactions were then reviewed by the investigator team. In case of a positive OFC with verified symptoms attributed to CMPA, infants were diagnosed with CMPA and remained on AAF. Infants who tolerated CMF during the challenges, in hospital and at home, were discharged from the study.

Safety data

Adverse events (AEs), serious and non-serious, during the study period were notified by the investigators and coded by diagnosis, severity, date of onset, and resolution. The investigators also assessed the causality of these AEs in relation to the study formula.

Ethics approval, study sponsorship, and oversight

The present study was approved by the Medical Ethics Committee of Hunan Children's Hospital, Hunan, China (HCHLL-2016-016). The overall conduct of the study was managed and supervised by a contract research organization (CRO), George Clinical, Sydney, Australia. The CRO monitored the clinical site set-up, investigator training, adverse event reporting, and data management. Independent statistical analysis was performed using Cytel, Cambridge, MA, USA. The study was sponsored by Nestlé Health Science, Vevey, Switzerland and registered on ClinicalTrials.gov (NCT03004729) prior to enrollment of the first patient.

RESULTS

Of the 301 infants screened, 254 progressed to the OFC (median age, 16.1 weeks; 150 [59.1%] male). One family withdrew before and 46 families withdrew during the AAF trial. The reasons for withdrawal were not consistently recorded. Infants presented with a range of symptoms, suggestive of non-IgE-mediated CMPA, and none of the infants presented with immediate symptoms. Atopic dermatitis and rectal bleeding were the most common presentations at enrollment. The clinical features at enrollment of the 254 infants who participated in the OFC are summarized in **Table 1**.

Table 1. Clinical presentation of infants with suspected cow's milk protein allergy

Clinical presentation	n	%
Atopic dermatitis	137	53.9
Rectal bleeding	39	15.4
Persistent diarrhoea	27	10.6
Regurgitation/vomiting	24	9.4
Constipation	9	3.5
Persistent crying/irritability	7	2.8
Poor weight gain	5	2.0
Respiratory symptoms	3	1.2
Feeding difficulties	1	0.4
Other/not documented	2	0.8
Total	254	100.0

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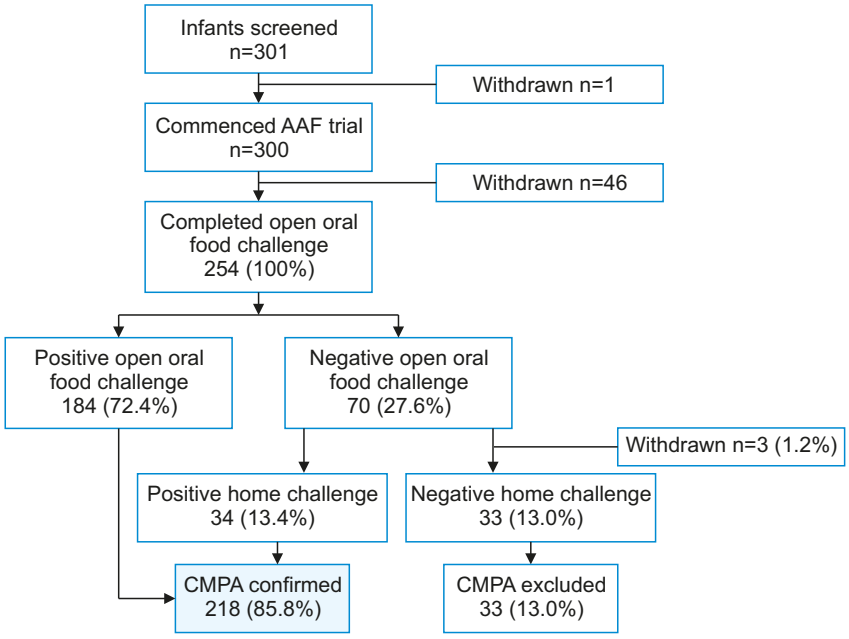

Fig. 1. Study flow chart.
AAF: amino acid-based formula, CMPA: cow's milk protein allergy.

Food challenge outcomes

Of the 254 infants who completed the OFC, 184 (72.4%) developed symptoms during the 4-hour hospital challenge on Day 1, and an additional 34 (13.4%) reacted during the home challenge. In total, 218 (85.8%) infants were diagnosed with CMPA. The study flow is summarized in **Fig. 1**.

Thirty-seven percent of infants had reactions involving multiple systems. The median eliciting dose of CMF was 3 mL (range 1–100), with significant variation across the clinical centers. Reactions during the OFC were generally mild to moderate in severity and the majority of reactions (174/184; 95%) included cutaneous manifestations, such as urticaria, increased redness/rash, or increased eczema. Thirty-eight (21%) infants presented with immediate respiratory reactions (persistent sneezing, cough, wheeze), and 29 (16%) had gastrointestinal reactions (nausea, food refusal, vomiting, diarrhea, or rectal bleeding).

Of the 70 infants who passed the OFC in the hospital, 67 proceeded with the 2-week home challenge, and three families withdrew from the study. Of these, 34 had clinical reactions that were deemed to be due to CMPA by the investigator. Twenty-two infants reacted during the first week and 12 infants during the second week of the home challenge. Reactions included exacerbation of eczema (n=26), recurrence of rectal bleeding (n=4), and frequent regurgitation (n=1). The reason for a positive home challenge was not documented in three infants.

Anthropometric measurements

Growth data were available for 217 of the 218 infants with CMPA. Of these, 126 (58.1%) were male. Age-adjusted mean Z scores for body weight, length, and HC calculated according to the WHO growth reference, confirmed that, as a group, infants maintained normal growth velocity from enrollment to 9 months of age (**Fig. 2**). The group means for WAZ, LAZ, and HCAZ tracked close to 0, and the mean of differences changed by less than 0.25 Z scores from enrollment to final visit (WAZ +0.207, LAZ +0.152, HCAZ +0.072) (**Table 2**).

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Table 2. Anthropometric measurements of 218 infants with open food challenge-confirmed cow's milk protein allergy

Time point	N	Age (wk)	Weight (kg)	WAZ	Length (cm)	LAZ	HC (cm)	HCAZ
Total cohort								
Birth	217	0	3.375±0.457	0.119±0.94	50.1±1.58	0.269±0.84	ND	ND
Enrollment	217	15.6±6.11	6.446±1.430	−0.029±1.35	62.6±4.63	0.400±1.49	40.1±2.21	−0.356±1.37
Final visit	211	40.0±2.85	8.923±1.251	0.178±1.25	72.7±3.00	0.552±1.36	44.2±1.63	−0.284±1.25
Male infants								
Birth	126	0	3.423±0.459	0.115±0.93	50.2±1.52	0.187±0.80	ND	ND
Enrollment	126	16.1±5.69	6.802±1.409	0.025±1.43	63.4±4.30	0.301±1.56	40.6±2.13	−0.406±1.44
Final visit	120	39.9±2.68	9.143±1.336	0.113±1.38	73.0±3.02	0.360±1.38	44.5±1.72	−0.455±1.34
Female infants								
Birth	91	0	3.308±0.449	0.123±0.97	49.9±1.63	0.383±0.88	ND	ND
Enrollment	91	14.9±6.63	5.953±1.314	−0.103±1.24	61.5±4.87	0.538±1.39	39.4±2.13	−0.285±1.28
Final visit	91	40.2±3.07	8.633±1.067	0.264±1.04	72.4±2.95	0.804±1.30	43.8±1.43	−0.059±1.09

Values are presented as mean±standard deviation.
WAZ: weight-for-age Z score, LAZ: length-for-age Z score, HC: head circumference, HCAZ: head circumference-for-age Z score, ND: no data.

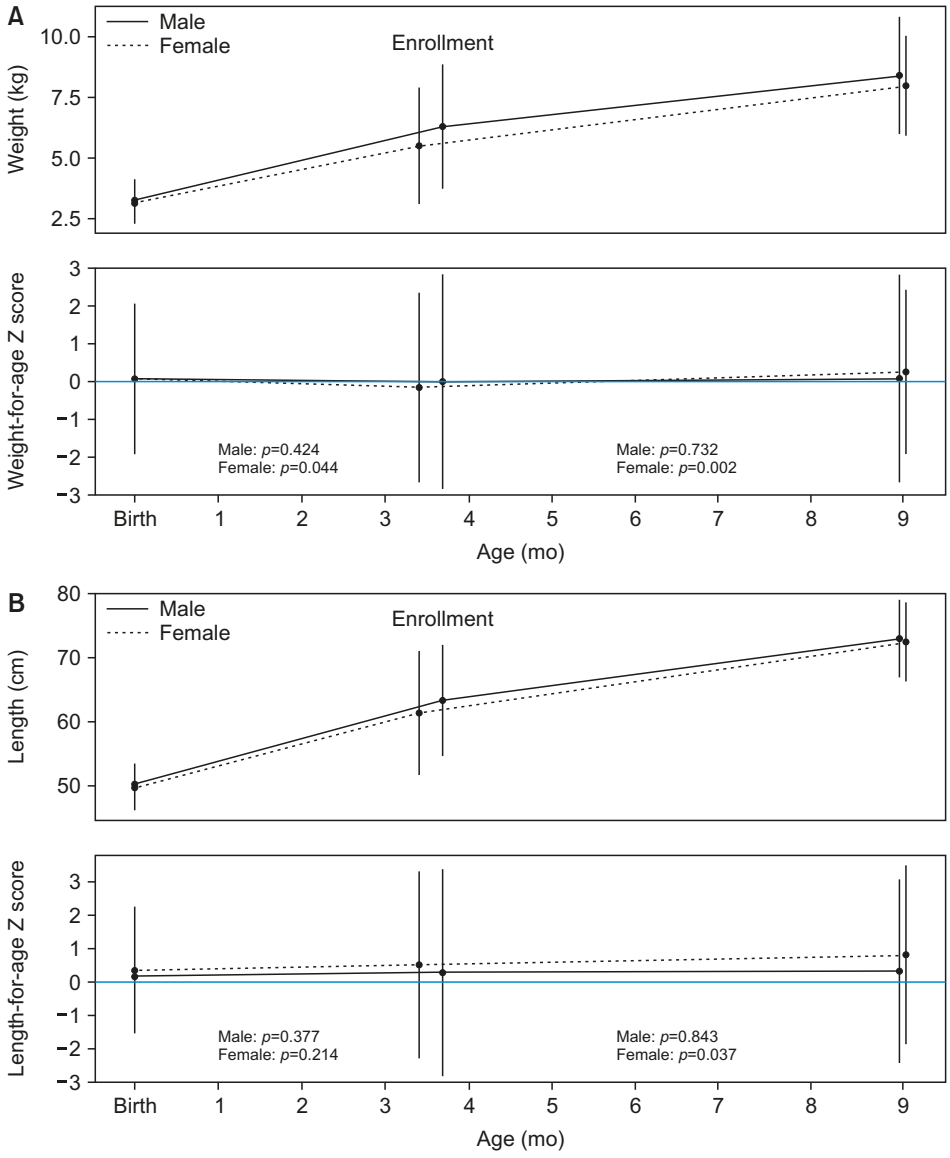

Fig. 2. (A, B) Mean weight/weight-for-age Z score (WAZ) and length/length-for-age Z score (LAZ) from birth to 9 months in 218 infants with challenge-confirmed cow's milk protein allergy. Error bars indicate the 95% confidence intervals for WAZ and LAZ. *p*-values are provided for paired *t*-test comparisons between birth and enrollment, as well as enrollment to final follow-up at 9 months of age.

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Overall, WAZ decreased from 0.119 to −0.029 between birth and enrollment (p=0.067) and increased from −0.029 to 0.178 (p=0.012) between enrollment and final visit at 9 months of age. The WAZ changes were greatest in female infants, in whom the mean WAZ decreased significantly from 0.123 to −0.103 (p=0.044) between birth and enrollment, with subsequent catch-up growth from −0.103 to 0.264 (p=0.002) between enrollment and 9 months. WAZ scores at birth and 9 months were similar (0.123 vs. 0.264; p=0.225). For male infants, there were no significant differences in WAZ between the time points (**Fig. 2A**).

LAZ scores for the entire cohort of infants with CMPA remained similar from enrollment to 9 months (0.400 vs. 0.552; p=0.214). However, in female infants, LAZ increased significantly from enrollment to final visit (0.538 vs. 0.804; p=0.037); there was no significant change in the male cohort. Furthermore, there were no significant differences in LAZ from birth to enrollment (0.269 vs. 0.400; p=0.147). There was a small but statistically significant increase in LAZ from birth to 9 months (from 0.269 to 0.552; p=0.003). This increase was mainly seen in the female cohort (0.383 vs. 0.804; p=0.002), whereas no such trend was observed in the male infants (0.187 vs. 0.360; p=0.205) (**Fig. 2B**).

There were no significant differences in the mean HCAZ scores between enrollment and final visit (−0.356 vs. −0.284; p=0.705). The mean HCAZ scores for male infants changed non-significantly from −0.406 to −0.455 (p=0.379), and for female infants increased slightly from −0.286 to −0.059 (p=0.133).

Safety data

There were 13 severe adverse events (SAEs) requiring hospitalization in 11 infants (bronchopneumonia/lower respiratory tract infection, n=8; gastroenteritis, n=2; Coxsackie virus infection, n=1; Kawasaki disease, n=1; cardiac malformation, n=1). All SAEs were deemed to be unrelated to the study formula. In addition, there were 207 non-serious AEs in 100 infants. These reported AEs were due to a range of conditions, including respiratory infection, 93 (44.9%); febrile illness/viral infection, 43 (20.8%); gastroenteritis/acute diarrhea, 24 (11.6%); functional problems (crying, dyspepsia, regurgitation, or constipation), 18 (8.7%); eczema flare/rash, 16 (7.7%); and in 13 (6.3%) by less common conditions. Four (1.9%) AEs were attributed as 'related' to the study product by the investigators (dyspepsia, n=1; eczema, n=1; perirectal abscess, n=1; diarrhea, n=1).

DISCUSSION

Our study examined the growth parameters in a large cohort of infants with challenge confirmed CMPA. To the best of our knowledge, this is the first such study performed in Chinese infants with CMPA. The diagnosis was established by 2-weeks strict CMP elimination while being fed an AAF, followed by a standardized OFC in the hospital and a 2-week open challenge at home, in this study. A diagnosis of CMPA was made in over 85% of the participating infants. Based on the spectrum of symptoms at enrollment, these infants suffered from non-IgE-mediated CMPA.

The group means of age-adjusted Z scores for weight, length, and HC at birth, enrollment at around 16 weeks of age, and the final visit at 9 months of age were close to 0. The anthropometric Z scores progressed in parallel with the 0 line, with changes in growth parameters within +0.25 standard deviations. The WAZ at the time of enrollment trended

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toward a slightly lower Z score, compared to birth, indicating mild weight loss secondary to CMPA. This decrease in WAZ was significant in the female infant cohort, who also achieved significant catch-up growth with the study formula by 9 months of age. This was associated with a small but significant increase in linear growth (LAZ) in female infants. There were no significant changes in WAZ, LAZ, or HCAZ in male infants in the present study. These findings strongly suggest that, as a group, infants maintained normal growth velocity, as well as linear and head growth velocity while being fed the study AAF, in conjunction with a CMP-free complementary diet.

The findings of the present study are in line with other studies in infants with CMPA that have also confirmed adequate growth while being fed an AAF [26-30]. In contrast, a recent review of growth patterns in healthy infants aged 0–4 months raised concerns that some hypoallergenic formulas may be associated with suboptimal growth [34]. This was mainly attributed to a high content of MCT exceeding 50% of total fat in some AAF or EHF products [34]. MCT are included in EHF and AAF to address possible fat malabsorption [35]. While MCTs are readily absorbed and utilized in the liver and muscle, they are minimally stored in fat tissue, which may explain the poor weight gain observed with high-MCT formulas in the first months of life [36,37]. The AAF used in the current study has an MCT content of 24%, and no evidence of growth impairment was observed in our cohort. However, our study design did not allow for a detailed assessment of the growth parameters in the first month of life.

The provision of adequate amounts of dietary protein is a prerequisite for normal growth during infancy. Most AAF contain relatively high levels of protein equivalent in the form of free amino acids, which exceeds the protein content in breast milk or standard infant formula. The rationale for this increased concentration is that not all amino acids may be absorbed and used as a source of nutrition. A high protein content in standard infant formulas has been linked to an increased risk of obesity in later childhood, but it remains unclear whether this also applies to AAF [38,39]. A systematic review did not detect evidence of accelerated growth in infants fed with an AAF [34]. In addition, a growth study in infants with CMPA managed with an AAF demonstrated normal growth till 12 months of age [29]. The present study provides additional normal growth data in infants fed an AAF up to 9 months of age, and no excessive weight gain was observed in our cohort.

The present study has several limitations. Data were collected as part of a large validation study of a possible diagnostic tool for CMPA, and growth was not the primary outcome. As a result, growth data were systematically collected only during the enrollment and study exit. In addition, formula volume intake and the contribution of the complementary diet were not documented. A further limitation is that the diagnosis of CMPA was not made by a double-blinded, placebo-controlled food challenge, which may have led to an overestimation of the rate of CMPA in our study. Despite these limitations, our study provides real-life growth data for a cohort of infants with challenge-confirmed CMPA.

In conclusion, our study demonstrates that Chinese infants with challenge-confirmed, non-IgE-mediated CMPA achieved normal weight gain, linear growth, and head growth while being fed the amino acid-based study formula, together with a CMP-free elimination diet, during the first 9 months of life. We did not observe evidence of excessive weight gain in our cohort, and we recommend further studies to assess the long-term effects of AAF on growth and body composition.

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